The Reproducibility of Activation Patterns in Patient and Control Populations: Measurement of Group and Subject Effects

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Introduction. We studied activation pattern reproducibility for a simple motor task using [^{15}O]water PET and linear discriminant analysis. Reproducible eigenimages (CEs)—obtained from a Canonical Variates Analysis (CVA) of the PCA eigenvectors from Scaled Subprofile Model (SSM) preprocessing—were identified by a twofold crossvalidation resampling technique [1]. Pattern similarity histograms were used to test for: (1) reproducible multidimensional subspaces, (2) reproducible patterns defined by between-subject effects and (3) the influence of individual subjects on pattern reproducibility in order to identify subgroups [of patients or controls] which increase or decrease reproducibility.

Methods. 18 right-handed controls and 14 patients with hereditary cerebellar ataxia (6 SCA1s , 8 SCA5s) were scanned while tracing a path along the perimeter of a five pointed star. Each scanning session consisted of 1 baseline trial (no tracing), 8 tracing trials and a final baseline. CE reproducibility was assessed for an SSM/CVA classification (**Exp. 1**) of 10 groups (10 scans/subject) reflecting the mean within-subject temporal structure of the 18 normal controls and (**Exp. 2**) of 4 groups, two defined by between-subject effects and two by baseline and tracing states. The four-group classification was applied separately to 14 randomly chosen controls (**Exp. 2a**) and to the 14 ataxia patients (**Exp. 2b**). In Exp. 1 each of the nine CEs for each of 250 randomly chosen training and test pairs (of independent groups of nine subjects) were correlated after reflection and reordering relative to an SSM/CVA of all 18 subjects (Fig. 1). Pattern similarity histograms for each of the three CEs from Exp. 2 are illustrated in Figs. 2a & 2b. In Exp. 2 each 7-subject group was randomly divided into two groups of three & four subjects; in Exp. 2b the groups were constrained to contain 3 SCA1 and 4 SCA5 patients/group. For **CE 2** in Exp. 1 and **CE 1** in Exp. 2b the least and most reproducible patterns from *each* of the 250 pairs of CEs were identified by correlating each pattern with the average CE of the pair with the largest r value. Subject influence was ranked by recording the number of times/250 pairs that each subject was included in the group producing the least reproducible pattern. This result was compared with the null hypothesis that subjects randomly contribute to groups with the least reproducible pattern, i.e., a binomial distribution, p=0.5 & N=250.

Fig. 1: 18 controls, 10 groups.

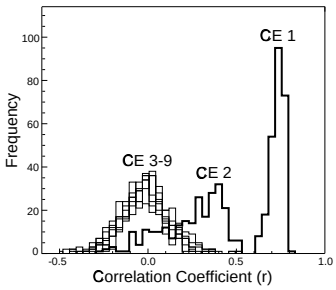


Fig. 2a:14 controls, 4 groups.

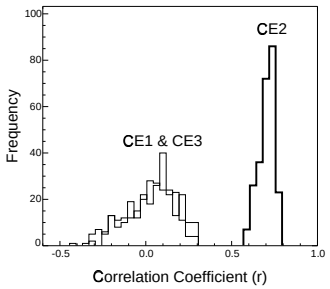
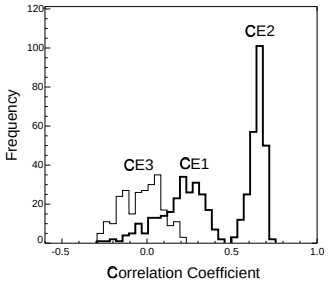


Fig. 2b:14 patients, 4 groups.



Results. In **Figure 1** the histograms for CE 3-9 are centered on zero reflecting no significant reproducibility of eigenimages 3-9, while CE 1's histogram and most of CE 2's histogram are significantly different from zero. CE 1's histogram reflects good reproducibility of a two-state baseline-tracing activation effect with no temporal tracing structure in the associated canonical variates. CE 1's average eigenimage contains the expected structures of the primary motor system. CE 2's canonical variates reflect a linear trend with time across the 10 scans/subject. Many pairs in CE 2's histogram have moderate reproducibility ($r \in [0.3,0.55]$) while some match the spread of the unreproducible patterns of CE 3-9's histograms. Ranking subject influence for CE 2 identified *5/18 subjects* that occurred more frequently and *3/18 subjects* that occurred less frequently than expected in the 9-subject groups with the least reproducible patterns (uncorrected $p < 0.05$). In **Figures 2a & 2b** the CE 2 histograms reflect good reproducibility of the two-state baseline-tracing activation effect (similar to CE 1 of Exp. 1) with only a slight reduction in the r-values for patients (Fig. 2b) compared to controls (Fig. 2a). In contrast the CE 1 histograms, which reflect between-subject group effects, depict no pattern reproducibility for subgroups of control subjects (Fig. 2a), but many patterns from SCA1 vs. SCA5 subgroups are moderately reproducible. Ranking subject influence for CE 1 in Exp. 2b identified *4/14 patients* that occurred more frequently and *6/14 patients* that occurred less frequently than expected in the between-subject groups with the least reproducible patterns (uncorrected $p < 0.05$). For a subgroup of patients there is a reproducible pattern reflecting SCA1 vs. SCA5 differences that may be distinguished from the basic baseline-tracing motor response.

Conclusions. We have demonstrated that pattern similarity histograms may be used to identify (1) reproducible multidimensional subspaces of activation patterns for within- and/or between-subject effects, (2) reproducible between-subject patterns of disease when the equivalent between-subject pattern in controls is nonreproducible and (3) subgroups of subjects that significantly influence group activation patterns making them more or less reproducible than expected.

Reference. Strother SC, Rehm K, Lange N, et al. (1998) Measuring activation pattern reproducibility using resampling techniques. In: Quantitative functional brain imaging with Positron Emission Tomography. Academic Press, San Diego, pp. 241-245